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10/582,327	06/09/2006	Mamoru Tsukada	03500.103828.	1626

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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
08/10/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/582,327	TSUKADA, MAMORU
	Examiner	Art Unit
	FRANK LU	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/7/2011*.	6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of RCE and the amendment filed on April 7, 2011 have been entered. The claims pending in this application are claims 2-4 wherein claim 4 has been withdrawn due to the restriction requirement mailed on February 17, 2010. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on April 7, 2011.

Claim Objections

2. Claim 3 is objected to because of the following informality: Tables 1-2 to 1-7 and 2-1 to 2-6 should be deleted because applicant does not select the probe set from Tables 1-2 to 1-7 and 2-1 to 2-6.

Appropriate correction is required.

Response to Arguments

In page 5, second paragraph of applicant's remarks, applicant argues that "[A]pplicant respectfully submits that Claim 2 is a generic claim linking the probe sets recited in Claim 3. Accordingly, rejoinder of Claim 3 is respectfully requested upon the allowance of Claim 2, pursuant to MPEP § 821.04(a)".

This argument has been fully considered but it not persuasive toward the withdrawal of the objection. First, since claim 3 has been examined by the Examiner (see the previous office actions), applicant's argument "rejoinder of Claim 3 is respectfully requested upon the allowance of Claim 2, pursuant to MPEP § 821.04(a)" is not correct. Second, since page 7 of the restriction requirement mailed on February 17, 2010 clearly stated that "[T]ables 1-1 to 1-7, 2-1 to 2-6, 5-1 to 5-9, 6-1 to 6-8, 9-1 to 9-4, 10-1 to 10-4, 13-1 to 13-3, 14-1 to 14-3, 17A, 17B-1, 17B-2, 18A, 18B-1, 18B-2, 21-1 to 21-8, 22-1 to 22-7, 27-1, 27-2, 28-1 and 28-2 read on patentably distinct probe set. Each probe set is patentably distinct because each probe set contains structurally unrelated sequences, and a further restriction is applied to each probe set. Applicant is advised that the examination will be restricted to only elected probe set and should not to be construed as a species election" and applicant has elected without traverse a probe set of Probe Nos. 0 and 1 from Table 1-1 (i.e., SEQ ID Nos: 251 and 252) in the reply filed on March 25, 2010, the examiner will not rejoin the non-elected subject matter recited in claim 3 and the examination in this instant case will only be limited to Group II, claims 2 and 3, and a probe set of Probe Nos. 0 and 1 from Table 1-1 (i.e., SEQ ID Nos: 251 and 252).

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. Claims 2 and 3 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claim 2, as written, do not sufficiently distinguish over nucleic acids which exist naturally because the claim does not particularly point out any non-naturally occurring difference between the claimed product and the naturally occurring nucleic acids. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303,206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Enablement

Claims 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a probe set comprising multiple probes that can be used for identification of an HLA-A allele contained in a specimen. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.,* 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of The Claims

Claim 2 encompasses a probe set comprising multiple probes that can be used for identification of an HLA-A allele contained in any kind of specimen under a condition in which any one of the multiple probes specifically hybridizes to the HLA-A allele wherein each of the multiple probes is a partial sequence of 10 to 30 successive bases of a sequence of an allele in the allele list for HLA-A in the specification, the partial sequence containing a base represented by a capital letter, and wherein the multiple probes, as taken all together and represented in small and capital letters as in the allele list for HLA-A, contain all the bases represented by capital letters in the allele list for HLA-A so that the 250 alleles of A*010101 through A*8001 listed in the allele list for HLA-A can be identified. Note that claim 2 does not indicate that a base represented by a capital letter and a base represented by a small letter have different structures. Claim 3 further limits claim 2 and requires that the probe set comprises SEQ ID NOs: 251 and 252.

Working Examples

The specification provides probes for identification of HLA-A alleles (see working examples 1 and 2 in pages 2-86 of US 2010/0028861 A1 which is US publication of this instant application). The specification provides no working example for identification of HLA-A alleles using the probe set comprising multiple probes under a condition in which any one of the multiple probes specifically hybridizes to the HLA-A allele wherein the multiple probes comprise SEQ ID NOs: 251 and 252 but include other probes which are not SEQ ID NOs: 251 and 252.

The Amount of Direction or Guidance Provided and The State of The Prior Art

Although the specification provides probes for identification of HLA-A alleles (see working examples 1 and 2 in pages 2-86 of US 2010/0028861 A1 which is US publication of this instant application), the specification does not provide a guidance to show that HLA-A alleles can be identified using the probe set comprising multiple probes under a condition in which any one of the multiple probes specifically hybridizes to the HLA-A allele wherein the multiple probes comprise SEQ ID NOs: 251 and 252 (16 and 21 nucleotides) but include other probes which are not SEQ ID NOs: 251 and 252. Furthermore, there is no experimental condition and/or experimental data in the specification to support the claimed invention. During the process of the prior art search, the examiner has not found any prior art which is related to identification of HLA-A alleles using the probe set comprising multiple probes under a condition in which any one of the multiple probes specifically hybridizes to the HLA-A allele wherein the multiple

probes comprise SEQ ID NOs: 251 and 252 (16 and 21 nucleotides) but include other probes which are not SEQ ID NOs: 251 and 252.

Level of Skill in The Art, The Unpredictability of The Art, and The Quantity of Experimentation Necessary

While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether HLA-A alleles can be identified using the probe set comprising multiple probes under a condition in which any one of the multiple probes specifically hybridizes to the HLA-A allele wherein the multiple probes comprise SEQ ID NOs: 251 and 252 (16 and 21 nucleotides) but include other probes which are not SEQ ID NOs: 251 and 252.

First, since claim 2 indicates that each of the multiple probes can be 10 to 30 nucleotides in length and does not require that each of the multiple probes has identical length and the specimen cannot be in a nitrocellulose membrane, it is known that synthetic oligonucleotides with different lengths such as 14, 17, 20, and 23 nucleotides require different hybridization conditions and different washing conditions when the synthetic oligonucleotides hybridize to DNAs on a nitrocellulose membrane (see Current Protocol in Molecular Biology, supplement 2, 6.4.1 to 6.4.10, 1993), under the condition in which any one of the multiple probes such as 10-bp oligonucleotide probe specifically hybridizes to the HLA-A allele, other of the multiple probes such as 21-bp oligonucleotide probe cannot specifically hybridizes to the HLA-A allele since, comparing with the hybridization temperature and the washing temperature of 10-bp oligonucleotide probe, the 21-bp oligonucleotide probe requires much higher

hybridization temperature and much higher washing temperature (see Current Protocol in Molecular Biology, supplement 2, 6.4.1 to 6.4.10, 1993).

Second, since human Neurl1B mRNA and SEQ ID NO: 252 are about 81% (ie., 80.95%) identical to nucleotides 169-189 (17/21) of human FLJ45422 mRNA (see the sequencing comparison between SEQ ID NO: 252 and human FLJ45422 mRNA in the office action mailed on December 7, 2010), SEQ ID NO: 252 can nonspecifically hybridize with human FLJ45422 gene under the condition in which any one of the multiple probes specifically hybridizes to the HLA-A allele wherein the any one of the multiple probes is 10-bp oligonucleotide probe. Therefore, it is impossible to identify HLA-A alleles in a specimen using the probe set comprising multiple probes without involving a nonspecific hybridization problem under a condition in which any one of the multiple probes specifically hybridizes to the HLA-A allele wherein the multiple probes comprise SEQ ID NOs: 251 and 252 (16 and 21 nucleotides) but include other probes which are not SEQ ID NOs: 251 and 252. Furthermore, nowhere in the specification provides a guidance to show that the probe set comprising multiple probes comprising SEQ ID NOs: 251 and 252 can be used to identify all 250 alleles of A*010101 through A*8001 listed in the allele list for HLA-A.

Third, since claim 2 does not indicate the number of the multiple probes, if multiple probes only have two probes, it is unclear how to identify 250 alleles of A*010101 through A*8001 based on the multiple probes such as two probes.

In view of above discussions, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test

whether HLA-A alleles in specimen can be identified using the probe set comprising multiple probes under a condition in which any one of the multiple probes specifically hybridizes to the HLA-A allele wherein the multiple probes comprise SEQ ID NOs: 251 and 252 (16 and 21 nucleotides) but include other probes which are not SEQ ID NOs: 251 and 252.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no guidance that leads one to claimed methods. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working example related to claimed invention recited in claims 2 and 3 and the no teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

In page 7, fourth paragraph of applicant's remarks, applicant argues that "[T]hese rejections are respectfully traversed, and are submitted to have been obviated by the amendments made herein".

This argument has been fully considered but it not persuasive toward the withdrawal of the rejection because applicant has not indicated why the amendments have overcome the rejection. Note that above rejection is different from the rejection made in the office action mailed on December 7, 2010 (see above rejection).

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 2 is rejected as vague and indefinite because it is unclear what sequence can be called as a sequence of each allele in an allele list for HLA-A in the specification. Please clarify.

Response to Arguments

In page 5, fifth and sixth paragraphs of applicant's remarks, applicant argues that "[A]pplicant respectfully submits that this language would be understood by one of ordinary skill in the art to refer to a sequence of one of the HLA-A alleles listed at page 15, line 9 to page 116, page 9 of the instant specification. In this regard, Applicant notes that the claims may refer to a listing in the specification where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating the listing in the claims. See MPEP § 2173.05(s)".

This argument has been fully considered but it not persuasive toward the withdrawal of the rejection because it is unclear what sequence can be called as a

sequence of each allele in an allele list for HLA-A in the specification since claim 2 has not indicated where the allele list for HLA-A is located in the specification. Furthermore, based on the examination purpose, it is impossible for the examiner to examine any of the HLA-A alleles listed at page 15, line 9 to page 116, page 9 of the instant specification.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. No claim is allowed.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG

94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571)272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Frank W Lu /,
Primary Examiner, Art Unit 1634
August 8, 2011